

Epigenetic changes in synaptic and inflammatory genes involved in the age-dependent development of Alzheimers disease pathologies andcognitive decline

<https://neurodegenerationresearch.eu/survey/epigenetic-changes-in-synaptic-and-inflammatory-genes-involved-in-the-age-dependent-development-of-alzheimers-disease-pathologies-andcognitive-decline/>

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USA

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Epigenetic changes in synaptic and inflammatory genes involved in the age-dependent development of Alzheimers disease pathologies andcognitive decline

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NIH (NIA)

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1

The project/programme is most relevant to:

Alzheimer's disease & other dementias

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Research Abstract

ABSTRACT Age is the greatest risk factor for the development of Alzheimer disease (AD). Thus, understanding the genetic and pathological mechanisms that underlie the age-dependent development of AD neuropathological change is critical to our ability to monitor and target these pathways. Histone modifications and DNA methylation have been suggested as epigenetic factors mediating the influence of environmental factors on AD-related gene expression. Trimethylated histone H3K9 (H3K9me3) is one of the key histone modifications associated with decreased transcriptional activity and heterochromatin condensation. We have found that H3K9me3 levels are significantly altered in neurodegenerative disease. Here, we propose an integrated analysis of H3K9me3- chromatin immunoprecipitation (ChIP)-sequencing (ChIP-seq), DNA methylation, and mRNA quantification on brain tissue to determine how heterochromatin remodeling driven by H3K9me3 and DNA methylation is altered in aging and AD and to define the epigenome profiles linked to AD pathogenesis. Our preliminary data shows that two major pathways are genetically silenced in AD, including one in synaptic function (e.g. brain derived neurotrophic factor (BDNF) and synaptotagmin XII (SYT12)) and one involved in neuroinflammation (e.g. interleukin 1 (IL1), phospholipase A2 receptor 1 (PLA2R1), and latexin (LXN)). We propose a translational approach to systematically address AD neurodegeneration in one of the best characterized autopsy cohorts of aging on the DNA, RNA, and protein levels, with the goal of identifying novel epigenetic risk factors, biomarkers, and mechanisms that can be targeted for drug discovery. The Framingham Heart Study (FHS) collects extensive clinical and neuropsychological data, follows a community-based population throughout their lifetime, and collects the brain at death. Neuropathologically, subjects range from cognitively normal to demented and from pathologically normal to low AD neuropathological change to high AD change. Novel, digitized neuropsychological tests allow for the earliest detection of cognitive decline. Our long-term goal is to uncover the epigenetic and molecular mechanisms underlying the development of AD and of healthy aging. The immediate goal of this research project is to discover differences in the epigenetic silencing of synaptic and neuroinflammatory genes that predict AD pathology and cognitive impairment and that may serve as biomarkers and targets for therapy. This research will be critical for understanding how epigenetic changes are associated with aging and the development of AD, informing rational drug design, and for developing ways to assess risk in aging individuals. We aim to link epigenetic and protein variation to the pathology of tau and A β in human subjects with a definitive pathological diagnosis and to the neuropsychological trajectory during life. Here we propose a cross-disciplinary approach that combines expertise and novel techniques in epigenetics, neuropathology, and cognitive testing to discover new pathogenic pathways for biomarker development and therapeutics.

Lay Summary

Project Narrative Histone modifications and DNA methylation are epigenetic factors that may mediate the influence of environmental factors on AD-related gene expression. The long-term goal of this research project is to uncover the epigenetic and molecular mechanisms underlying the development of AD and of healthy aging. The immediate goal is to discover differences in

the epigenetic silencing of synaptic and neuroinflammatory genes that predict AD pathology and cognitive impairment and that may serve as biomarkers and targets for therapy.

Further information available at:

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Investments > €500k

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United States of America

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Alzheimer's disease & other dementias

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